Cancer of the Cervix, Vulva and Vagina

JAMES F. NOLAN, M.D., Los Angeles

THE PURPOSE of this Chapter is to discuss the clinical aspects of cancers involving the uterine cervix, vulva and vagina. Since tumors of the lower genital tract have certain common characteristics they may be considered together. However, differences in clinical behavior in relation to their anatomic distributions lead to differences in recognition and management. For this reason they are usually discussed as separate entities. Since cervical carcinoma may be considered the primary problem of the lower genital tract it will be presented first so that the pertinent features of vulvar and vaginal cancer may be compared.

Carcinoma of Cervix

Carcinoma of the uterine cervix is the most important malignant tumor of the pelvic genitalia, primarily because of its frequency. It is the most common such cancer and its incidence has been reported as 13 per cent of all cancers in the female, 52 per cent of all genital cancers in women. In recent years the absolute incidence of the disease in its invasive form appears to be decreasing. There is a tendency to attribute this decrease to the early recognition and treatment of the tumor in its pre-invasive stage. However, other factors cannot be discounted.

As far as etiology is concerned, the exact causative agent and the effect of environmental situation or genetic influence are not known. Most epidemiologic investigations indicate a relatively high incidence in persons in the lower socio-economic strata. There is some indication that the incidence of the disease is related to early sexual and reproductive activity. However, the etiologic features of the disease are not clearly delineated, despite intensive study.

Carcinoma of the cervix uteri is primarily a pre-menopausal and menopausal disease. The average age at the time of diagnosis is about 48 years. However, it sometimes occurs in the early 20s, and in elderly patients it is still more frequent than carcinoma of the corpus uteri, although the latter is primarily a post-menopausal disease. Classically, invasive cervical cancer is thought to be preceded by a pre-invasive or *in-situ* stage. This clinical entity appears in patients whose average age is 38 years or some ten years earlier than invasive cancer. Actually, the pre-invasive disease is more frequent than the invasive, so that progression may not always be complete or regression of the pre-invasive lesion may occur in some instances. From a clinical standpoint, however, the time elements involved in progression from a pre-invasive tumor to an invasive one, allow for recognition in the earlier phase and the application of definitive treatment, which is usually highly effective.

If we assume that epidermoid cancer develops from a pre-invasive lesion over a long period, at some time the supporting fibromuscular stroma is invaded. The site of this change is classically at the junction of the glandular epithelium of the endocervix and the squamous epithelium of the portio. Usually, this site is at the external os of the cervix but may vary in individual instances, so that it may be on the face of the portio itself or be higher, within the cervical canal. In the latter instance, a cervical tumor may be covert and not recognizable on direct inspection.

With rapidly growing cells the first pathologic process is tumefaction, but in gross there may be no great change because of shedding of the surface cells. Eventually a mass appears which is surrounded by normal tissue. These tissues respond with a desmoplastic reaction in an attempt to wall off the rivaling tumor. In most instances this reaction is abortive or incomplete. Sooner or later cords and sheets of malignant cells spread beneath the mucosal surfaces and deeply into the surrounding tissues. Invasion by direct extension will follow the course of least resistance, and the classic pattern of spread is between the supportive connective tissue structures at the base of the broad ligament in a lateral direction toward the pelvic walls.

In addition to spread by direct extension, lymphatic permeation and spread may be superimposed. Lymphatic channels are plentiful in and around the cervix uteri and the main trunks pass laterally along the courses of the uterine vessels to the primary lymph nodes in the parametrium. These nodes are in relation to the great vessels in the pelvis along

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the lateral pelvic walls. Secondary lymphatic spread may occur to the inguinal areas or cephalad to the periaortic regions outside the true pelvis. In addition to these methods of extension there may be vascular spread to distant parts of the body.

In the usual course of events, however, local extension and pelvic lymph node involvement put the ureters at risk. Constriction of these structures by growing tumor results in stasis, infection and eventual renal damage. The result of local tumor growth is to produce uremia secondarily and oftentimes exitus occurs before distant metastasis becomes manifest. Complications other than uremia may occur. Prolonged bleeding leads to anemia and inanition; secondary infection leads to parametritis and pelvic peritonitis; extrinsic pressure on bowel leads to obstruction and toxemia; and lymphatic obstruction leads to lymphedema of the lower extremities, vulva and abdomen. All these processes result in considerable disability and pain over a chronic course unless uremia intervenes.

There are three cardinal symptoms: Abnormal bleeding, abnormal discharge and pain. A cervical tumor may slowly outgrow its support and then suddenly slough, with massive hemorrhage. However, the usual history is that of small amounts of painless bleeding not in relation to the menses. Post-coital bleeding is a common complaint and it may occur in the early phases of the disease. Although irregular bleeding is the most frequent complaint, the amount or type of bleeding cannot be correlated with the extent of the disease because of variations in the growth characteristics of individual tumors. An exophytic growth may produce a sizable hemorrhage and still be in an early stage of development. Conversely, an infiltrative tumor may be far advanced and yet not be ulcerated enough to cause extensive bleeding. Thus, a direct correlation between this symptom and prognosis cannot be made.

Carcinoma of the cervix may be associated with a thin, watery discharge which is usually an early symptom but, unfortunately, the amount and type of discharge is fairly innocuous and ordinarily does not disturb the patient. In later stages when secondary infection appears, the discharge may be thicker and perhaps odorous. This is more noticeable to the patient but is a poor prognostic sign because secondary infection may contribute to tumor spread or at least interfere with adequate treatment.

The third symptom of pelvic pain usually connotes advanced disease and a poor prognosis. Deep, constant pelvic pain may be due to nerve root involvement by direct extension of the tumor. Secondary infection with parametritis and pelvic peritonitis, too, may cause pain. As stated, both these situations indicate extensive tumor advancement and are associated with late recognition of the tumor.

The diagnosis of cervical cancer, like that of other malignant diseases, is made definitely on the pathologic examination of excised tissue. However, the physical examination and certain diagnostic aids are most important.

In most cases of advanced lesions, gentle but thorough digital examination and inspection will result in a presumptive diagnosis of cancer, but verification by biopsy is needed to rule out chronic ulcerative or granulomatous lesions. On the other hand, patients presenting themselves because of symptoms must be examined thoroughly even though no obvious tumor is demonstrable in order to disclose an advanced covert lesion or an incipient change.

One of the most important advances in cancer control in the present era, widely used and practical for screening purposes, is the "Papanicolaou smear" examination. This is the cytologic study of exfoliated cells which may be indicative of a malignant change even though no overt lesion is demonstrable. Another diagnostic aid is the "Schiller test." It is done by painting the cervical portio and vaginal fornices with Lugol's solution. The normal mucosa stains a dark brown, but abnormal or suspicious areas do not stain because of lack of glycogen. The "Clark test," also helpful, entails gentle stroking of the endocervical canal with a sound. If brisk bleeding occurs, it merely indicates friability but increases suspicion of a hidden endocervical tumor. Colposcopy is a procedure to inspect the epithelium in vivo by magnification under direct vision. This procedure too will show suspicious areas which may need further study by biopsy.

Although originally it was proposed that the material for examination be obtained by aspiration from the vaginal pool, greater "yields" of early malignant changes have been produced by direct wiping of the endocervix and portio. Since the latter technique demands direct visualization of the cervix, it is more time-consuming than aspiration. Still, it is a simple and painless procedure which can be performed in the course of a routine office examination. Not only is cytologic examination becoming more and more accepted by the medical profession in general and by pathologists in particular, it has also been popularized among the laity. This has been an important development in the diagnosis of cervical cancer because the acceptance of this test has led to more persons presenting themselves for examination and hence the recognition of early tumors which can be controlled by adequate treatment.

In general, however, it is important to reiterate that definitive diagnosis is still a matter of histologic

rather than cytologic examination because of several limitations to the study. Smears may be read as negative, suspicious or positive, and classified in categories from one to six. Sometimes, because of secondary infection, necrosis or poor preservation of the cells, smears may be "negative" in the face of grossly obvious cancer. "Positive" smears may result from cellular atypia following previous radiation treatment or infection. "Suspicious" smears may appear with atrophy and secondary infection. It must be borne in mind that patients cannot be expected to evaluate the results of the test for themselves: A "negative" report may make them overly confident that no cancer exists; a "suspicious" report, which may be the result of a physiologic rather than a pathologic change, may frighten them unnecessarily. Furthermore, a report of "Class I or II," which is negative for cancer, may be interpreted by the patient as indicative of cancer. It is important, then, for all concerned to realize the limitations of such testing and to correlate the results with the symptoms and physical findings in the individual patient. Certainly, it is not wise to initiate definitive and radical treatment for cancer upon the basis of a single cytological examination alone. Periodic vaginal smear examination is strongly recommended.

Suspicious or positive results may be confirmed and usually further investigation and office biopsy will reveal the lesion. Such procedures are usually simple and painless and seldom are accompanied by complications. In the face of a positive smear, repeated examination will reveal a tumor which can be biopsied with the usual punch forceps or indicate an endocervical lesion which can be simply curetted. In such fashion the definitive diagnosis can be made. However, there are certain instances where a smear has been reported as positive and biopsies are negative; or in which repeated smears are suspicious in spite of clearing of local infection and atrophic changes. On such occasions it becomes necessary to proceed to a more diagnostic attempt by performing a fractional curettage and "cold knife" conical excision of the cervix under anesthesia.

It is important, with such a procedure, that all the tissues to be examined are carefully collected and preserved in order to accomplish the purpose of the study. However, wide conical excision of the cervix is not an innocuous procedure. Oftentimes it may be followed by hemorrhage of gross proportions and may later result in cervical stenosis. If a definitive diagnosis can be made without resorting to extensive measures it is usually the wiser course. Extensive trauma to and cauterization of an invasive tumor may result in necrosis, in secondary infection, in later hemorrhage and perhaps in extension of the lesion locally. In general, the most information one can acquire with the least trauma seems to result in the greatest tumor control.

After definitive diagnosis by histopathologic examination, most tumors are classified by one or more means with the intention of assessing their prognosis. In the case of carcinoma of the cervix uteri, there are several types of classifications which are used. Of course, the histologic type is first noted and usually this tumor is epidermoid in character but may be an adenocarcinoma in about 5 per cent of the instances. Although some observers believe the glandular type of cancer may carry a poorer prognosis, it is probable that results of treatment are essentially the same, depending more upon the gross extent of the lesion than the histologic type. In addition, these tumors may be further classified as to the degree of de-differentiation or anaplasia of the histologic morphology. This is conventionally called the "grade," and a tumor showing a high degree of anaplasia is usually indicative of a poorer prognosis than is a more differentiated tumor. However, in carcinoma of the cervix, with the usual means of treatment, the histologic grade does not seem to have a great prognostic significance. This is due to the fact that most of the tumors show little maturity and perhaps other factors have more of an influence which overshadows this characteristic.

The growth type of the tumor, too, may be used as a method of classification. Exophytic or outgrowing tumors seem to respond more favorably to treatment than endophytic or infiltrative lesions. An ulcerated lesion may not respond to treatment as well as an exophytic one, but perhaps better than an infiltrative lesion, depending upon the type of tumor from which it arose.

The clinical characteristic most closely associated with prognosis seems to be the gross extent of the tumor. This is evaluated usually by clinical examination before treatment is initiated and conventionally is referred to as the "stage" of the lesion. There have been several such classifications, but the one commonly accepted is the International (or League of Nations) classification. Briefly, it includes: Stage I—those lesions which involve the cervix alone. Stage II—lesions involving the cervix, parametria without fixation to the pelvic wall, and/or the vagina without extending to its lower one-third, and/or the uterine corpus. Stage III—lesions which are fixed to the pelvic wall and/or involve the lower one-third of the vagina. Stage IV—lesions extending beyond the true pelvis or to the mucosa of bladder or rectum, or showing distant metastasis. This gross classification can be subdivided into further classifications to differentiate large and small invasive tumors of the cervix; those that involve the parametria or the vagina primarily; or those which show generalized dissemination, as compared to mucosal

involvement of the adjacent organs. Further, the pre-invasive lesions may be separately classified as Stage O. These special classifications refer to cervical cancer only; they have the advantage of being universally accepted but they have the disadvantage of being complicated.

The State of California Tumor Registry uses a gross classification which is simpler and may be applied to malignant tumors of all sites. Stage I is localized to the primary organ; Stage II shows regional extension or lymphatic spread, and Stage III is disseminated tumor. In California statistical reports on carcinoma of the cervix, in-situ or pre-invasive lesions are included as Stage I. This is not true for the International statistics collected at Stockholm.

As far as treatment is concerned, the general philosophy is to apply radical measures as a primary therapeutic attempt in invasive cancer. The limitations of clinical evaluation as to the exact extent of the lesion, as well as the known propensity for even grossly early tumors to show inperceptible lymphatic metastasis, demand that all patients be treated as if extension has already occurred. The almost universal failure of secondary treatment measures, after incomplete primary attempts, emphasizes the necessity for "radical" application of therapy in the first instance.

Modifications of this general philosophy occur mainly in the management of pre-invasive tumors. If there is adequate evidence that the lesion in question is totally in-situ aand there is a desire to preserve reproductive function, such cervical lesions can be managed by conservative means. Dilatation and curettage, wide conical excision and continuous follow-up examination will allow for maintenance of the reproductive function in young persons. Because of the long interval usually assumed in the development of true or invasive cancer and the efficacy of diagnostic measures in recognizing pre-invasive changes from cytologic studies if they should remain or reappear, such controlled management entails little risk. This is especially true in young women, in whom in-situ changes are much more frequent than invasive cancer.

In women in the menopausal or post-menopausal years this is not true. Invasive cancer is much more frequent than the pre-invasive lesion. Here there is no question of maintaining reproductive or even ovarian function. Although some investigators advise conservative measures in all instances of carcinoma-in-situ, usually in older persons the treatment is radical, as though the lesion were an early invasive one.

Pre-invasive cancer usually is recognized in women in their late thirties and early forties. Since most of them have fulfilled their reproductive functions and still have some years of expected ovarian function, the common mode of management is complete hysterectomy with ovarian preservation. Radiation therapy would ablate the ovaries, and conservation of the cervix would leave some doubt as to complete control in the future, so that surgical management remains the most widely used method of treatment. It must be emphasized, however, that the removal of the uterine corpus does not completely eradicate the cellular changes in the area at risk. It is also necessary to remove any suspicious or non-staining epithelium on the portio or in the vaginal fornices if the procedure is to be technically adequate. Further, it is necessary to continue clinical observation and cytologic studies in order to recognize a residual or new malignant process in the apex of the vaginal vault.

In most areas the general method of management of invasive carcinoma of the cervix is by radiation methods. Most techniques include external irradiation from an x-ray machine or tele-cobalt apparatus, as well as intracavitary radium or other radioisotope applicators. These modalities are combined to deliver theoretically adequate doses of radiation throughout the entire pelvis to include the areas at risk.

The combination of external and intracavitary methods must be carried out in a planned fashion so that dangers from complications due to over-irradiation, as well as under-irradiation, may be avoided.

In general, the local radium application seems to be the most important phase in early tumors, and the external radiation phase of treatment is the most critical in the advanced lesions. In the latter instance, if there is evidence of extensive tumor spread, it is necessary to deliver large amounts of radiation in a uniform distribution throughout the large tissue volumes involved. In the early cases, doses pushed beyond optimal and tolerable limits may result in excessive numbers of distressing complications without improving chances of tumor control and survival.

Although the exact techniques are complicated, adequate apparatus and personnel are available in nearly all areas of this country, so that expert radiation therapy may be applied.

Some physicians prefer surgical therapy to radiation in the management of early invasive cervical cancer. The operative approach again is radical and technically includes extirpation of the lymphoid tissues along the pelvic vessels, the parametria and the upper vagina as well as the uterus and adnexa. The main technical difficulty lies in the management of the ureters and the bladder base, which are within the lines of excision. Injury to these structures or to the blood vessels supplying them may result in distressing complications. Although over-

all results from management of this type in select cases are similar to those for radiation therapy in comparable cases, the incidence of major complications is much higher. For this reason radiation therapy is the method of treatment most often used.

There are variations in the primary radical approach to management which have had variable popularity. Combinations of surgical and radiation modalities have been proposed through the years. Generally speaking, the improvement in results obtained by radical excision after radical radiation therapy is not enough to warrant the more extensive complications usually associated with this method. The normal tissues which must support the extensive trauma of both methods of treatment are unable to recover satisfactorily. Because of this there have been modifications directed at reduction of the amount of radiation or of surgical trauma. Results from such modifications have not proved to be superior to those from primary radical operation or radical radiation therapy alone. Along these lines there has been a renewed interest in the radical vaginal hysterectomy of Schauta. This technically difficult procedure is effective in control of local tumor and its vaginal extension, but does not allow for lymph node dissection. The latter must be performed as a secondary retroperitoneal lymphadenectomy, or the nodal areas must be subjected to extensive secondary radiation therapy in order to fulfill the principles of tumor control.

Results of treatment seem to be steadily improving over the years. Apparent five-year survival rates for the pre-invasive form approach 100 per cent in treated series regardless of the method of management. Moreover, the results of treatment for invasive cancers have improved steadily, not only because of the gradual increase in the proportion of patients who are treated when the tumor is in an early stage but also because of improvement in treatment techniques.

As reported from Stockholm, the International collected results of treatment (five-year survival) of carcinoma of the cervix for the years 1950 to 1954 inclusive, are as follows: Stage I, 73.2 per cent; Stage II, 51.2 per cent; Stage III, 26.7 per cent; Stage IV, 7.3 per cent.

Prophylaxis is a most important feature in the management and control of this disease. If we understood the etiologic background of the disease process, it is possible that many cases could be avoided. Continued interest in epidemiology and case reporting may give us pertinent information. Extensive efforts to diagnose the premalignant and pre-invasive phases of the disease process, when it is amenable to fairly simple therapeutic measures, seem fruitful. Certainly continued improvement through the use of exfoliative cytology and more frequent pelvic examination is to be expected. The fact that early stages of the invasive disease respond so much better than late stages makes increased suspicion as to the cause of symptomatology on the part of physicians and laity most important. Educational programs have been directed at this phase and have been effective. As far as treatment techniques are concerned, increased interest in radio-physics and radio-biology has certainly been important in a gradual improvement in results. Extended surgical procedures have been explored and found effective in control of very extensive or secondarily recurrent tumors, even though the over-all yield in survivals has been low insofar as comparison to the morbidity, mortality and over-all effort is concerned. So far, the use of adjuvant chemotherapy has been important only in palliative management, but certainly we can hope for more effective treatment measures in the future. In general, however, future improvement in tumor control seems based on the increased interest in the disease and a change from late, difficult treatment problems to early, more amenable tumors through early diagnosis.

Carcinoma of Vulva

Carcinoma of the vulva is the fourth most frequent malignant disease of the pelvic genitalia. It represents less than 1 per cent of all cancers in the female and 3 per cent of all genital cancers. It is primarily a post-menopausal disease. The average age of patients is 60 years.

Etiologically, it has been associated in the past with a concomitant incidence of syphilis, but this does not seem to hold in recent years. Usually it is thought to be a degenerative process because of its association with the atrophic changes in the post-menopausal years. There has been some recent interest in the association of this malignant disease with condylomata appearing in earlier years and treatment by sclerosing medications or low voltage x-rays. However, it is difficult to ascertain whether condylomata may be precursors to malignant change or the treatments were carcinogenic. The situation is similar to that in carcinoma of the cervix in that the cause is far from certain but interest in etiologic features is prominent.

The usual pathologic feature in association with vulvar cancer is leukoplakia—white patches on the vulva, which occur in association with about 50 per cent of the instances of vulvar cancer. The process is thought to be pre-malignant. There is some confusion as to what leukoplakia actually represents grossly, because such white patches may appear with vitiligo, tinea cruris, lichen planus et atrophicus and other diseases. However, the leukoplakia which is thought to be a precursor to cancer

is described as lichen hypertrophicus, since there is not only atrophy of skin folds but also hyperkeratosis in the epidermis. Certainly vulvar cancer does not develop in all patients with leukoplakia, but at least it seems to be a precursor in many instances.

From the pathologic standpoint the entire vulva must be considered a single organ. It is subjected to various traumata of reproduction and of infection, and is responsive to hormonal stimuli. The epidermal structures covering the labia major and minora, the clitoris and vestibule, as well as the lining of the Bartholin ducts and glands, are subject to malignant changes. The usual atrophy and subsequent premalignant changes may involve parts or all of these structures. The extensive lymphatic circulation in these areas, with drainage to the superficial and deep inguinal nodes and contralateral connections, makes malignant tumors at these sites more difficult to manage than such lesions on other skin surfaces.

In the usual course of events, one or more areas will slowly proceed through a pre-malignant to a pre-invasive malignant transformation. Eventually invasion into the submucosal or subcutaneous tissues will occur, with tumefaction and later ulceration. Direct extension into vagina, urethra and anus will occur with partial obstruction and secondary infection. Superimposed upon these processes, lymphatic involvement will cause vascular obstruction, edema of the lower extremities, and nerve root pain. The process of development and extension is slow and usually is accompanied by considerable discomfort because of proximity of the lesion to the excretory orifices. Prominently one sees secondary infection, fistula formation, ulceration, hemorrhage and gradual inanition. Distant metastasis may occur but death is usually a result of the local destructive process.

The most frequent presenting symptom of a patient with vulvar cancer is pruritis. Of course, pruritis may be a symptom of a number of benign conditions and it may result from concomitant conditions rather than from the cancer itself. Ulceration with hemorrhage is a later symptom which may be associated with trauma or scratching of the vulva. Urinary difficulty, bowel obstruction and lymphedema are all late complaints and indicate a poor prognosis.

Diagnosis again depends upon complete visual and digital examination and biopsy upon the recognition of a lesion. In most instances, biopsy may be done as a simple office procedure with local anesthesia and without complication. Before treatment is considered, suspicious areas of leukoplakia or tumor should be tested by biopsy lest an incomplete procedure be carried out or an unnecessarily radical treatment be applied.

It should be noted that although it would seem the pruritis, bleeding or mass associated with vulvar cancer would disturb the patient enough to make her seek medical aid early, this is not generally true. Often embarrassment or ignorance or optimism causes long delay. Furthermore, some physicians are reluctant to examine elderly, excessively modest patients thoroughly, deferring biopsy of these easily accessible lesions in favor of conservative, symptomatic treatment with hormones, topical medication and various types of physiotherapy.

As in cervical cancer, after diagnosis, vulvar tumors may be variously classified. Usually the tumor is epidermoid histologically, but occasionally an adenocarcinoma which arises from the Bartholin gland may be present. The histologic grade of the tumor may again be classified according to the degree of differentiation. Many of these tumors are fairly mature, and there seems to be some correlation between this feature and ultimate prognosis.

As far as gross features are concerned, classifications may be made as to the site of origin of these tumors. Thus, they may be designated as: labial, preputial, vestibular, clitoral or vulvo-vaginal gland types.

Assessment of the gross extent of the lesion is made in some form of staging. There is no generally accepted classification in vulvar cancer as there is in cervical cancer, but in general the following characteristics are used:

Stage I—Small lesions under 3 cm in diameter.

Stage II—Lesions over 3 cm in diameter but not extending to urethra, vagina or anus and without palpable inguinal nodes.

Stage III—Lesions showing clinical evidence of extension to adjacent structures, or grossly involved inguinal nodes.

Stage IV—Disseminated disease, fixed locally to adjacent organs or with fixed technically irremovable nodal involvement.

As in other malignant diseases the simple gross staging utilized by the State of California Tumor Registry may be applied. Again, the three stages of localized tumor, regional or nodal involvement, and disseminated or metastatic disease, are applicable.

As to prognosis, there is definite correlation between ultimate outcome of treatment and the gross extent of the tumor at the time of application.

The primary method of management of vulvar cancer is surgical. In scope the operation should include the entire primary organ and the tissues in the areas of lymph node extension. The classical operation now is a one-stage radical vulvectomy with bilateral superficial and deep lymph node dissection. Local excision of the tumor, partial or unilateral

vulvectomy, and the like are obviously incomplete procedures and usually are inadequate because of the profuse lymphatic network in and around the vulva. However, as the accepted classical procedure is an extensive one, it may be too traumatic for some of these elderly patients. For this reason various modifications toward conservatism have been advocated. One-stage bilateral superficial groin dissection and vulvectomy has been suggested for patients considered poor operative risks. The addition of the deep dissection of the secondary nodes may not add appreciably to the salvage if they be involved but it does add to the difficulty of the operation, to the severity of complications and to the length of convalescence.

Other modifications may be to perform the vulvectomy and node dissection in two or three stages, allowing for recovery and local healing after each.

In some instances of Stage I tumors of low histologic grade in obese, aged or debilitated patients, the surgeon may elect to do vulvectomy only, deferring groin dissection until clinical evidence of involvement has occurred.

All such modifications will obviously be detrimental to the chance of survival for the patient, but must be considered when the constitutional condition of the patient will not permit the accepted radical method of management. It is only in cases of limited leukoplakic or in-situ carcinoma that simple vulvectomy is considered adequate. This procedure must be extended to encompass the entire organ and areas of perianal skin which have undergone change.

Radiation therapy has not been as effective as surgical excision in the management of carcinoma of the vulva. Although the tumors themselves may be responsive to ionizing radiation, the surrounding vulvar area cannot tolerate intensive radiation injury. The skin folds and excretory orifices are usually moist, contaminated and subject to excessive maceration, which limits their tolerance. The same is true of the inguinal areas to a lesser degree. However, in many instances, because of extension of the disease beyond the scope of adequate excision, or because of constitutional complications, vulvar carcinomata may be managed by radiotherapy.

Often irradiation with radium applied locally by the use of plaques or molds or by interstitial implantation will give good local control. Inguinal areas can be treated with protracted techniques and with supervoltage generators which have advantages in their "skin-saving" characteristics. Even with advanced lesions, satisfying palliative results may be obtained by meticulous radiotherapy, so this modality should not be completely abandoned.

When one considers the possibilities of management and control of this disease in the future, the first consideration must be that of prophylaxis. In vulvar cancer the word *prophylaxis* has practical meaning because of the association of leukoplakic vulvitis with subsequent carcinoma. A leukoplaque is oftentimes symptomatic, can be observed easily and a specimen for biopsy easily obtained, and is amenable to treatment. Treatment by topical applications, hormone creams and low frequency radiations is usually not efficacious, but simple vulvectomy is applicable. This operation, when performed adequately, is not too difficult technically nor too disfiguring anatomically to apply more frequently than it is.

Early diagnosis of vulvar cancer is difficult mainly because of the reluctance of patients to consider the possibility of the disease and to present themselves for examination. Further, physicians in general apparently are not as alert as they ought to be to cancer at that site.

As far as treatment is concerned, efforts can only be made to increase the physician's concern as to the seriousness of these lesions and the necessity for as radical management as possible within the limitations of the patient's constitutional condition.

At present, the usual five-year survival data show an over-all rate of 36 per cent. The California data show five-year survival for the various stages as: Stage I, 60 per cent; Stage II, 16 per cent; Stage III, less than 10 per cent. It is obvious that vulvar cancer if treated while in localized stages carries a fairly acceptable prognosis.

Carcinoma of Vagina

Primary vaginal cancer is extremely rare. The reported incidence as shown by data from the California Tumor Registry is less than 1 per cent of all genital cancers and 0.2 per cent of all carcinoma in females.

Usually these tumors occur in post-menopausal patients and the most common sites are the upper vault and the fornices. It has been suggested that chronic discharge and irritation have a causative influence, but in view of the rarity of this disease and the frequent occurrence of discharges, this seems unlikely.

Primary vaginal cancer is usually an epidermoid tumor. It develops as either a unicentric or a multicentric lesion in the vault. It may appear as an *in situ* or superficial lesion; eventually it spreads submucosally and invades. If it appears in the upper vault, extension is along the base of the broad ligament; if it begins in the lower half, it may spread into the vestibule and vulva. Because of the proximity of the bladder and urethra anteriorly and the rectum posteriorly, direct invasion of these organs occurs early in the course of the disease. Superimposed upon direct extension of this kind is the

possibility of lymphatic permeation and spread. In the case of lesions of the upper half of the vaginal vault, lymphatic spread follows the same routes as do lesions primary in the cervix; spread of tumors in the lower half may follow vulvar routes. In addition, mid-vaginal tumors may spread into the perirectal lymphatic channels and circumscribe the rectum to the posterior sacral nodes.

Growing tumors will eventually ulcerate and bleed. They are prone to secondary infection which may result in pelvic cellulitis. Involvement of the bladder and rectum will result in obstruction and/or fistula formation, and in cases in which the patient dies death is usually owing to complications of local involvement.

In addition to epidermoid carcinoma, another rare primary cancer of the vagina is the mixed Mullerian sarcoma of infants, *sarcoma botryoides*, so named because on gross examination it has a grape-like appearance. This cancer is extremely rare and exceedingly malignant, growth filling the vagina and invading bladder and rectum promptly. Vascular metastasis to distant sites occurs in most cases.

Symptoms associated with vaginal cancer are, again, leukorrhea, abnormal vaginal bleeding and pain. Leukorrhea, as in carcinoma of the cervix, may occur in early stages but is not dramatic enough to concern the patient. The abnormal bleeding is also similar to that in carcinoma of the cervix; it is frequently post-coital. The significance of pain is similar to that of cervical cancer. Moreover, pain may indicate bladder or bowel involvement and obstruction.

Suspicion raised in reference to symptoms demands thorough investigation with adequate palpation, visualization and biopsy of demonstrable lesions. The exact site of a lesion in the vault may be difficult to demonstrate. Examination in the knee-chest position and the use of Lugol's staining are frequently helpful. Smears can be important, as exfoliated cells may be available for collection and examination.

Classifications again are helpful. These include the histologic grade and the gross extent of the disease—the "stage." The former cannot be directly correlated with prognosis because of the rarity of the disease, hence the paucity of data. The extent of the growth of course has great prognostic significance.

Primary carcinoma in the upper vaginal vault is usually treated by radical radiation therapy. External radiation is similarly applied but application of radium must be individually designed to encompass the local tumor. Bombs and interstitial needle implantations are frequently useful. In most instances the entire vault must be irradiated and special vaginal applicators have been designed for this purpose. These are especially useful in treating mid-vaginal lesions. In lesions of the lower half the primary treatment may be surgical, the principles being the same as for vulvar cancer. However, many of these lesions are advanced or show local extension into bladder and rectum. In such instances extended surgical procedures, such as anterior, posterior or complete exenteration must be considered.

Prognosis is generally poor in this disease. The California Tumor Registry does not have data on survival for any large series.

As far as future management and control of the disease are concerned, the same principles must be applied here as in the other diseases previously discussed. Hopes for improvement in prognosis can only be realized by finding lesions early. Hence the need for a high degree of suspicion and increased care in examination and testing.

1407 South Hope Street, Los Angeles, California 90015.